

DOI: 10.21767/2248-9215.100013

Hemoglobin A1c and Umbilical Cord Components: Prediction of Fetal Macrosomia in Women with Gestational Diabetes Mellitus

Esraa H AL-Maini¹, Layla H Hamad², Nadia D Yassir¹ and Samera H Hamad³

¹Department of Obstetrics and Gynecology; AL-Yarmouk Teaching Hospital, AL- Mustansiriya University, College of Medicine, Baghdad, Iraq

²Department of Obstetrics and Gynecology; Baghdad Teaching Hospital, Bab Al-Muadham, Baghdad, Iraq

³Department of Behavioral and Community Health; the University of Maryland, School of Public Health, College Park, USA

Corresponding author: Samera H Hamad, Department of Behavioral and Community Health; the University of Maryland, School of Public Health, College Park, USA, Tel: +608-217-3839; E-mail: shamad@umd.edu

Received Date: March 25, 2017; **Accepted Date:** April 10, 2017; **Published Date:** April 20, 2017

Copyright: © 2017 Hamad SH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: AL-Maini EH, Hamad LH, Yassir ND, et al. Hemoglobin A1c and Umbilical Cord Components: Prediction of Fetal Macrosomia in Women with Gestational Diabetes Mellitus. *Eur Exp Biol.* 2017, 7:13.

Abstract

Objectives: This study aims to understand the importance of the glycated hemoglobin (HbA_{1c}) levels and umbilical cord components in prediction of fetal macrosomia.

Methods: Ninety pregnant women (45 women with diabetes mellitus and 45 women with no diabetes mellitus) were chosen to measure the HbA_{1c} level and ultrasound umbilical cord components during their 36th to 37th weeks of pregnancy.

Results: Significantly higher ($p < 0.01$) HbA_{1c} levels, with higher umbilical cord components (Wharton's jelly) ($p < 0.01$) were observed in macrosomic fetus of diabetic women compared with control group. 16 of 45 (36%) of diabetic women had macrosomic fetuses; 11 of them had HbA_{1c} > 45 mmol/mol and 5 women had normal HbA_{1c} levels. 12 of 45 (27%) of non-diabetic women had constitutionally macrosomic fetuses with normal HbA_{1c} levels.

Conclusions: The relationship between the umbilical cord components and the birth weight was not specific for the diabetic group. Macrosomic fetuses could be predicted more accurately by the combination of both birth weight and the umbilical cord components (i.e. Wharton's jelly).

Keywords: HbA_{1c}; Wharton's jelly; Diabetic women; Macrosomia

Introduction

Fetal macrosomia is a risk factor for delivery complications for mothers and newborns [1]. It is associated with the gestational diabetes, but can occur in other pregnancies. About 2-9% of all pregnant women are diagnosed with gestational diabetes [2]. The American College of Obstetricians and Gynecologists (ACOG) defines macrosomia as a birth weight that is >4,000 g

irrespective of gestational age, or >90th percentile for gestational age after correcting for neonatal sex and ethnicity [3]. Health professionals have used ultrasound-derived estimated fetal weight and glycated hemoglobin (HbA_{1c}) levels to predict the risk of macrosomia during pregnancy [4]. However, these findings still have not received a consensus agreement on the accuracy of both approaches. Additionally, professional groups disagree on whether to recommend routine screening, selective screening based on risk factors for gestational diabetes, or no screening [2,5,6]. Given the serious problems that might be associated with delivery of the macrosomic fetus, identification of at risk fetuses and treatment of gestational diabetes to control the maternal glucose levels are both important risk-reduction strategies.

Sonographic prediction of fetal weight in large for gestational age fetuses based on weight estimation equations is associated with overestimation and the reliability of these methods, has been questioned by some authors [7,8]. Studies have shown that the use of umbilical cord components and glycated hemoglobin (HbA_{1c}) levels can give more accurate results to predict macrosomia [4] while others showed that HbA_{1c} levels cannot be used to predict macrosomia [9]. Study the agreement of both approaches is important to predict macrosomia. Therefore, we aimed to understand the importance of measuring HbA_{1c} along with umbilical cord components by sonographic examination in prediction of macrosomia in women with gestation diabetes mellitus.

Methods

Participants

Randomly, ninety pregnant women were divided into two groups: 45 diabetic women (study group) and 45 non-diabetic women (control group), were included in the study. Examination of pregnant women took place in AL-Yarmouk Teaching Hospital, Baghdad, Iraq from August 2015 to August 2016, during routine antenatal assessment. All pregnant women included in this

study were in the third trimester of a singleton pregnancy. All diabetic women (study group) were diagnosed with gestation diabetes mellitus and treated with insulin. Oral glucose tolerance testing (OGGT) was used to test the control group.

The gestational age was calculated based on the last menstrual period and confirmed measurement of crown-rump length and second trimester ultrasound at <20 weeks. Pregnant women with ruptured membrane, and multiple pregnancies, medical disorders (e.g. Renal, cardiovascular diseases, pulmonary diseases or/and hypertension), Polyhydramnios or oligohydramnios, Intrauterine growth retardation, placenta previa and abruption, fetal congenital abnormality or smoker, were all excluded from this study. Verbal consent was obtained from each woman before the examination. A complete evaluation for each pregnant woman was done including detailed history of age, gravidity, parity, history of previous diabetes mellitus, hypertension or any medical diseases and a previous delivery of large baby. The diagnosis of gestational diabetes was depending on the Oral Glucose Tolerance Test (the American Diabetes Association criteria). HbA_{1c} levels were measured for all both groups (study and control). The study protocol was approved by Obstetrics and Gynecology committee of Arabic Board for medical specialization and the hospital administration.

Ultrasound examination

Both groups of pregnant women were subject to ultrasonographic examination. During ultrasound examinations, fetal anthropometric parameters, biparietal diameter, abdominal circumference, femur length and estimated fetal weight (which were calculated automatically according to Hadlock's formula) were measured. Additionally, the sonographic cross-sectional areas of the umbilical cord and the umbilical vessels were measured in a free loop of the umbilical cord using ultrasound machine with convex transducer frequency of 3.5 Megahertz (Philip, HD 11 XE). The cross-sectional area of Wharton's jelly was computed by subtracting the cross-sectional area of the vessels from that of the umbilical cord. Fetal macrosomia was considered to be present when neonatal weight was equal or higher than 4,000 g [3].

HbA_{1c} analysis

Hemoglobin A1c is defined as the hemoglobin that is irreversibly glycated at one or both N-terminal valines of the beta chains [10,11]. 3 ml of venous blood samples were collected from each woman, placed in anti-coagulant tube (tubes with EDTA). Immunoturbidimetric method (standardized by DCCT: Diabetes Control and Complications Trial and certificate by NGSP: National Glycohemoglobin Standardization Program) [12] was used to determine total hemoglobin calorimetrically using alkaline hematin.

Babies' body weight

After delivery, babies' body weights were assessed using the neonatal scale.

Statistical analysis

Regression model embedded in Microsoft Excel 2010 was used to compare the results of umbilical cord components and the levels of HbA_{1c} in diabetic pregnant women with those in non-diabetic women. Results are considered to be statistically significant if p-value is less than 0.05.

Results

The demographic characteristics of diabetic and non-diabetic pregnant women are presented in **Table 1**. Results show that the mean age, gravity and parity were significantly higher in diabetic women than non-diabetic women. Gestational age at delivery was not statistically different; but the rate of cesarean section was significantly higher (71%) for women with diabetes compared to women with no diabetes mellitus (13%). These results are concordant with what has been previously published [13]. Vaginal delivery showed lower rate (31%) for diabetic women compared to non-diabetic women (69%).

Table 1 Demographic characteristics of diabetic and non-diabetic pregnant women.

Name	Diabetic patients (Mean value)	Non diabetic patients (Mean value)	p-Value
Age (year)	31.5	26.2	<0.05
Gravidity* (n)	3.4	2.6	<0.05
Parity** (n)	2.4	1.6	<0.05
Fetus weight (g)	3,340	3,040	<0.05
Gestational age at delivery time (week)	38.4	38.6	NS***
Cesarean section n (%)	32 (71%)	14 (31%)	<0.01
Vaginal delivery n (%)	13 (29%)	31(69%)	<0.01

*defined as the number of times that a woman has been pregnant
 **defined as the number of times that she has given birth to a fetus with a gestational age of 24 weeks or more, regardless of whether the child was born alive or was stillborn
 *** Not Significant

Table 2 Umbilical cord components of diabetic (n=45) and non-diabetic pregnant women (n=45).

Patients		Mean ± STD	p-Value
Cross sectional area of umbilical cord (mm ²)	Study group	282 ± 50	<0.05
	Control group	208 ± 31	
Umbilical cord thickness (Wharton's jelly) (mm ²)	Study group	164 ± 52	<0.05
	Control group	127 ± 26	

Results of umbilical cord components of the diabetic women (study group) and non-diabetic women (control group) were presented in **Table 2**. Mean value of cross sectional area of umbilical cord of study group was significantly (p<0.05) higher in

women with diabetes mellitus compared with the control group (Figure 1). Wharton's jelly was also significantly higher ($p < 0.05$) in the diabetes mellitus group compared to control group.

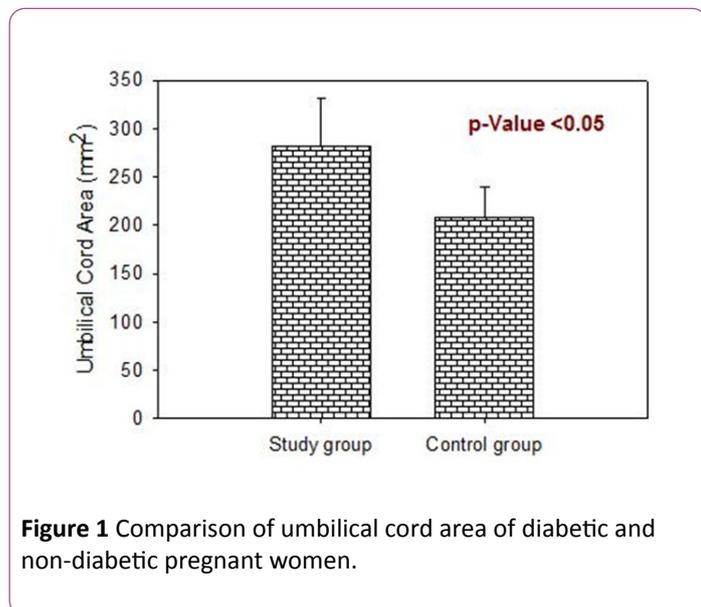


Figure 1 Comparison of umbilical cord area of diabetic and non-diabetic pregnant women.

HbA_{1c} levels are presented in Table 3. Results show that 11 of 45 diabetic women had HbA_{1c} higher than 45 mmol/mol; five women had an HbA_{1c} between 30 mmol/mol and 45 mmol/mol; and 29 women had HbA_{1c} that is lower than 30 mmol/mol. Additionally, HbA_{1c} levels were related with the weight of the fetus. Table 3 show that 16 of 45 (36%) of diabetic women had macrosomic fetuses; and 11 of them (69%) had HbA_{1c} that is higher than 45 mmol/mol. In the control group (non-diabetic pregnant women), there has been 12 of 45 (27%) of the cases that had constitutionally macrosomic fetuses.

Table 3 HbA_{1c} levels for diabetic pregnant women related macrosomia.

	Number of cases (n)	HbA _{1c} (mmol/mol)	Weight of fetus (g)
Diabetic pregnant women n=45	11	≥ 45	≥ 4,000*
	5	30 < x < 45	
	29	≤ 30	≤ 3,450
Non-diabetic pregnant women n=45	12	≤ 27	≥ 4,000
	33	≤ 25	3,000 ≤ x ≤ 3,250

*Weight of fetus that is >4,000 g, is an indicator of macrosomia

Regression lines showed correlation ($R^2=0.55$) between fetus weight and Wharton's jelly (umbilical cord thickness); and good correlation ($R^2=0.84$) between fetus weight and HbA_{1c} levels in 16 of 45 diabetic women. Correlation was also found between the weight of fetus and Wharton's jelly ($R^2=0.68$) with no correlation between fetus weight and HbA_{1c} levels ($R^2=0.34$) in 29 of 45 diabetic women (Figure 2). No correlation was found among these variables (i.e. fetus weight, Wharton's jelly, and HbA_{1c} levels) in the control group (data is not shown here).

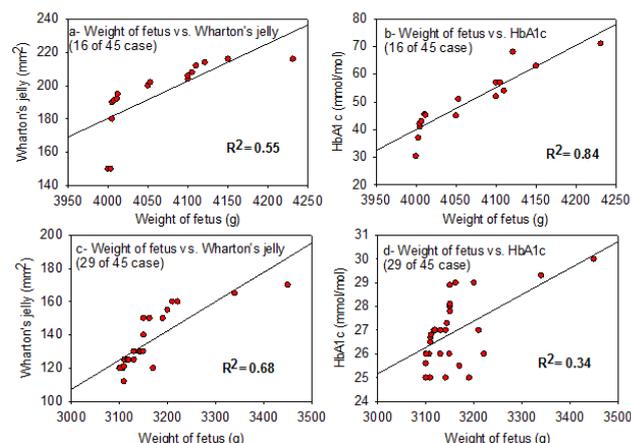


Figure 2 Regression line of fetus weight versus Wharton's jelly (umbilical cord area mm²) and HbA_{1c} levels in 16 (a and b), and 29 (c and d) of 45 of diabetic pregnant women.

Discussion

Infant macrosomia was a mediating factor in high cesarean delivery rate for women with diabetes. This study shows that 16 of 45 diabetic women delivered macrosomic infants. Additionally, 12 of 45 cases in the control group (women with no diabetes mellitus) delivered constitutionally macrosomic infants. Cesarean section rate in diabetic women was higher than that for the control group (32(71%) versus 14(31%)); these results agreed with what has been published before [14].

It has been found that the large umbilical cord area is attributed to the large amount of Wharton's jelly in diabetic mothers; this was attributed to the increase in the permeability of umbilical vessels in diabetes mellitus that increases the plasma protein leakage in the interstitial space [15].

Our results show that the infant of diabetic mother has large umbilical cord area due to a large amount of Wharton's jelly. This might differentiate between the appropriate-for-gestational-age fetus from a normal pregnancy and that from a pregnancy in a mother with gestational diabetes, and between the macrosomic fetus of a diabetic pregnancy from the genetically large fetus [15].

Association between HbA_{1c} levels and risk of macrosomia has been investigated before [9,16,17]. However, positive correlation was found between HbA_{1c} levels and risk of macrosomia in some studies [16,17]; while other studies showed no association between the levels of HbA_{1c} and risk of macrosomia [9]. Our results showed that 16 of 45 of diabetic pregnant women had macrosomic fetuses, and 11 of them had high HbA_{1c} (Table 3). This study combined the HbA_{1c} levels with the umbilical cord components (i.e Wharton's jelly) to increase the sensitivity of prediction of macrosomia [4]. The weight of macrosomic fetuses of diabetic mothers showed positive correlation with the HbA_{1c} levels (Figure 2b). This has been further confirmed by the positive correlation between the weight of macrosomic fetuses and the umbilical cord area (Wharton's jelly) (Figure 2a) which

imply that, in addition to the umbilical cord components, HbA_{1c} levels could also be used to predict macrosomic fetuses [18]. Although, positive association was found between the weight of fetuses and the umbilical cord components in 29 of 45 of diabetic mothers (**Figure 2c**), no association was observed between the weight of fetuses and the HbA_{1c} (**Figure 2d**). However, there was no macrosomia in these cases and the HbA_{1c} level was normal (**Figure 2c and 2d**).

Acknowledgment

Authors would like to thank the staff of clinical biochemistry department at AL-Yarmouk Hospital for their help in HbA_{1c} analysis.

References

- Mohammadbeigi A, Farhadifar F, Soufi Zadeh N, Mohammadsalehi N, Rezaiee M, et al. (2013) Fetal macrosomia: risk factors, maternal, and perinatal outcome. *Ann Med Health Sci Res* 3: 546-550.
- Hoffman L, Nolan C, Wilson JD, Oats JJ, Simmons D (1998) Gestational diabetes mellitus-management guidelines-The Australasian Diabetes in Pregnancy Society. *Med J Aust* 169: 93-97.
- Ng SK, Olog A, Spinks AB, Cameron CM, Searle J, et al. (2010) Risk factors and obstetric complications of large for gestational age births with adjustments for community effects: results from a new cohort study. *BMC Public Health* 10: 460.
- Binbir B, Yeniel AO, Ergenoglu AM, Kazandi M, Akercan F, et al. (2012) The role of umbilical cord thickness and HbA_{1c} levels for the prediction of fetal macrosomia in patients with gestational diabetes mellitus. *Arch Gynecol Obstet* 285: 635-639.
- Seshadri R (2002) American diabetes association gestational diabetes mellitus. *Diabetes Care* 25: S94-S96.
- Solomon MJ, McLeod RS (1994) Periodic health examination, 1994 update: 2. Screening strategies for colorectal cancer. Canadian Task Force on the Periodic Health Examination. *CMAJ* 150: 1961-1970.
- Sokol RJ, Chik L, Dombrowski MP, Zador IE (2000) Correctly identifying the macrosomic fetus: improving ultrasonography-based prediction. *Am J Obstet Gynecol* 182: 1489-1495.
- Hirata GI, Medearis AL, Horenstein J, Bear MB, Platt LD (1990) Ultrasonographic estimation of fetal weight in the clinically macrosomic fetus. *Am J Obstet Gynecol* 162: 238-242.
- Katon J, Reiber G, Williams MA, Yanez D, Miller E (2012) Antenatal haemoglobin A1C and risk of large-for-gestational-age infants in a multi-ethnic cohort of women with gestational diabetes. *Paediatr Perinat Epidemiol* 26: 208-217.
- Jeppsson JO, Kobold U, Barr J, Finke A, Hoelzel W, et al. (2002) Approved IFCC reference method for the measurement of HbA_{1c} in human blood. *Clin Chem Lab Med* 40: 78-89.
- Hoelzel W, Miedema K (1996) Development of a reference system for the international standardization of HbA_{1c}/glycohemoglobin determinations. *J Int Fed Clin Chem* 8: 62-64, 66-7.
- No authors (2016) IFCC Standardization of HbA1c. NGSP.
- Ovesen PG, Jensen DM, Damm P, Rasmussen S, Kesmodel US (2015) Maternal and neonatal outcomes in pregnancies complicated by gestational diabetes. A nation-wide study. *J Matern Fetal Neonatal Med* 28: 1720-1724.
- Naylor CD, Sermer M, Chen E, Sykora K (1996) Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? Toronto Trihospital Gestational Diabetes Investigators. *JAMA* 275: 1165-1170.
- Weissman A, Jakobi P (1997) Sonographic measurements of the umbilical cord in pregnancies complicated by gestational diabetes. *J Ultrasound Med* 16: 691-694.
- Mikkelsen MR, Nielsen SB, Stage E, Mathiesen ER, Damm P (2011) High maternal HbA_{1c} is associated with overweight in neonates. *Dan Med Bull* 58: A4309.
- Baxi L, Barad D, Reece EA, Farber R (1984) Use of glycosylated hemoglobin as a screen for macrosomia in gestational diabetes. *Obstet Gynecol* 64: 347-350.
- Holmstrom SW, Botelho J, Downes K, Lynch C (2012) Hemoglobin A1C as a Predictor of Fetal Macrosomia. *J Women's Health Care* 1: 11.